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New insights into the global burden of noroviruses and opportunities for prevention

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Noroviruses are now recognized as the leading cause of acute gastroenteritis across the age spectrum. New global estimates of the norovirus disease burden highlight the specific populations most affected and potential targets for prevention strategies. As traditional infection control and food hygiene measures may be inadequate to fully control norovirus disease, vaccines are an appealing option. Initial trials of candidate vaccines have demonstrated only modest efficacy, but show promise that norovirus prevention through vaccination is possible. Key issues that require further study include duration of immunity, degree of cross-protection, and efficacy in target populations. While initial introduction of norovirus vaccines is likely to occur in developed countries, the greatest public health burden and thus potential impact of such vaccines is in developing countries.

Recognition of the public health impact of noroviruses has increased dramatically in the past two decades through the application of molecular-based diagnostics. In many developed countries, noroviruses are now recognized to be the leading cause of acute gastroenteritis across the age spectrum and the leading cause of foodborne disease, including outbreaks [1]. In the United States, for example, noroviruses are responsible for approximately 20 million episodes of acute gastroenteritis annually, with about 70,000 hospitalizations and up to 800 deaths, mostly in the elderly [2]. Furthermore, following the decline in rotavirus disease after vaccine introduction in 2006, noroviruses have replaced rotavirus as the leading cause of severe gastroenteritis in US children aged <5 years [3]. However, from a global perspective, the greatest public health burden from noroviruses is undoubtedly exacted upon developing countries, where diarrheal diseases remain among the leading causes of death [4]. A recent systematic review concluded that norovirus was associated with 18% of all acute gastroenteritis worldwide [5]. Of 175 studies included in the review, 147 (84%) were

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published since 2008, among which 94 (64%) were conducted in developing countries. While data specifically on norovirus incidence and disease burden from these countries are more limited and some studies have suggested that detection of noroviruses may not be causally associated with illness in all cases [6,7], this review demonstrates the increased effort in recent years to better understand the public health impact of noroviruses globally so that we may better address it.

In 2015, the World Health Organization (WHO) released the first global estimates of the burden of foodborne disease [8]. Noroviruses were identified as the leading global cause of foodborne illness and among the top five causes of foodborne disease–associated death. Worldwide, the WHO estimated that noroviruses annually cause 685 million cases of diarrhea (95% confidence interval [CI]: 491 million–1.1 billion) and 212,489 deaths (95% CI: 160,595–278,420), with ~85% of these illnesses and ~99% of the deaths occurring in developing countries [9]. The Southeast Asia and Africa regions alone accounted for ~85% of all norovirus deaths. Much of this illness was in older children, adults, and the elderly with only ~30% of norovirus illnesses and ~25% of norovirus deaths in children aged <5 years. Of note, in developed countries with prolonged life expectancy, most of the deaths were in the elderly, whereas in low-income countries, much of the disease and death were in children aged <5 years. In the Africa region, for example, children aged <5 years comprised ~60% of all norovirus cases. These landmark WHO estimates provide an important opportunity to assess currently available prevention strategies for noroviruses, which have traditionally focused on infection control and food hygiene. However, while noroviruses are the leading cause of foodborne disease worldwide, direct exposure to contaminated food is estimated to account for <20% of all norovirus cases [10,11]. As such, improvements in food safety without addressing the underlying transmission in human population reservoirs may be inadequate in fully controlling norovirus disease. Vaccines may, therefore, provide a useful tool for effectively addressing the global burden of noroviruses.

Multiple norovirus vaccines are currently in the pipeline, although the one that is the furthest along in clinical development is an intramuscular bivalent genogroup GI.1/GII.4 virus-like particle (VLP) formulation. A clinical trial among healthy adults given this vaccine and then challenged with heterovariant GII.4 virus failed to demonstrate significant reduction in the overall incidence of norovirus disease (22% efficacy, 95% CI: −44–58%); however, the vaccine did significantly reduce norovirus disease severity as measured by a modified Vesikari score [12]. Additionally, vaccine recipients tended to clear the virus more rapidly than those receiving placebo, suggesting that vaccine may afford some additional benefit in terms of subsequent transmission risk. An initial proof-of-concept trial using an intranasal monovalent genogroup GI.1 VLP formulation followed by homologous viral challenge had demonstrated somewhat better efficacy, with 47% (95% CI: 15–67%) reduction in norovirus disease incidence and 26% (95% CI: 1–45%) reduction in norovirus infection [13]. While these early trial results demonstrate room for improvement in vaccine performance, they provide hope that in the future a vaccine could reduce the global burden of norovirus disease.

Several key questions remain, however, such as the degree of cross-protection given the diversity of noroviruses and continual emergence of new strains and the duration of vaccine-

induced immunity. While the majority of norovirus disease worldwide is caused by a single genotype, GII.4 [11,14], new variants within this group have emerged every 2–4 years over the last two decades, apparently driven by escape from population immunity [15]. These 'GII.4 du jour' strains generally replace their predecessors but co-circulate with up to 30 other norovirus genotypes, which may be antigenically distinct [16]. The selective pressures behind these dynamics indicate that norovirus infection does confer at least some acquired immunity, suggesting that vaccine-induced immunity may likewise be possible. However, an effective norovirus vaccine may require multiple constituent antigens as well as periodic reformulation to adapt to changes in molecular epidemiology. Additionally, immunity following norovirus infection is not lifelong and estimates of the duration of immunity vary widely from 6 months to 9 years [17,18]. Assuming a vaccine affords similar duration of protection as natural infection, vaccine boosters may be necessary given the impacts of norovirus disease across the age spectrum, particularly among young children and the elderly. Potential issues with immunosenescence in the elderly and other host-specific factors may also impact vaccine performance and need to be assessed through further study.

Additional data addressing issues of immunity, along with more refined estimates of disease burden, can help inform future development of effective norovirus vaccine programs, including the specific groups that should be targeted. Given the highly infectious nature of noroviruses, their propensity for causing outbreaks, and their primary reservoir being in humans, it is possible that a vaccine intervention could afford both direct benefit to vaccine recipients and indirect benefits to others through prevention of downstream transmission. For example, a vaccine that directly reduces norovirus incidence in children, who have the highest rates of norovirus disease, may help decrease exposure and subsequent severe outcomes among the elderly, as has been observed following rotavirus vaccine introduction [19]. However, more data are needed on potential vaccine efficacy in different age groups, as well as the possible role of herd protection and other transmission dynamics. Other potential targets for norovirus vaccines may be prioritized due to high disease burden (e.g. travelers and military), transmission risk to others (e.g. health-care workers and food handlers), or both (e.g. immunocompromised patients) [20]. While initial licensure and introduction of norovirus vaccines is likely to occur in developed countries, their greatest potential benefit lies in developing countries. The collective body of science on noroviruses that has amassed over the last two decades demonstrates a global public health need for norovirus vaccines and serves as a call for further efforts to address key remaining issues so that their potential benefits, particularly to the most impoverished countries of the world, may soon be realized.

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